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The Transcriptional Regulation of Human LRWD1 through DNA Methylation

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Abstract : Leucine-rich repeats and WD repeat domain containing 1 (LRWD1) is highly expressed in the testes of healthy males. On the other hand, LRWD1 is significantly down-regulated in the testicular tissues of patients with severe spermatogenic defects. In our study, the downregulation of LRWD1 expression by shRNA caused a significant reduction of cell growth and mitosis and a noteworthy increase in the cell microtubule atrophy rate. Here, we used EMBOSS CpG plot analysis to explore the promoter region of LRWD1 gene. We found that CpG islands are located between positions -253 to +5 nucleotides upstream from the LRWD1 transcription start site. Luciferase reporter assay revealed that the hypermethylation of the LRWD1 promoter reduced the transcription activity in cells. In addition, quantitative methylation-specific PCR and immunostaining showed that the methylation inhibitor, 5-Aza-2'-deoxycytidine, increased LRWD1 promoter activity, LRWD1 mRNA, protein expression and cell viability. Whereas, the methylation activator, S-adenosylmethionine, caused opposite effects. The overexpression of p53 and Nrf2 in NT2/D1 cells increased LRWD1 promoter activity while 5-fluorodeoxyuridine decreased it. In conclusion, this study highlights evidence that the methylation status of LRWD1 promoter is associated with LRWD1 expression. Since the expression level of LRWD1 plays an important role in spermatogenesis, the methylation status of LRWD1 may serve as a novel molecular diagnostic or therapeutic approach in male's infertility.

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